PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Gunnar Leo KARUP, et al.

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For: NOVEL RALOXIFENE ACID ADDITION SALTS AND/OR SOLVENTS THEREOF, IMPROVED METHOD FOR PURIFICATION OF SAID RALOXIFENE ACID ADDITION SALTS AND/OR SOLVATES THEROF AND PHARMACEUTICAL COMPOSITION COMPRISING THESE

SUPPLEMENTAL SUBMISSION REGARDING SUBSTITUTE SPECIFICATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

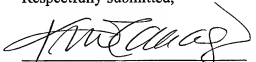
Sir:

Submitted herewith is a Substitute Specification (clean copy) and Substitute Specification (marked-up copy).

These versions were taken from an electronic version sent to the undersigned on behalf of the Inventors. While the pagination somewhat differs from the original Specification, the content is the same.

I further state that I have reviewed the changes in the Substitute Specification and do not believe any change constitutes new matter.

Respectfully submitted,



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Novel raloxifene acid addition salts and/or solvates thereof, improved method for purification of said raloxifene acid addition salts and/or solvates thereof and pharmaceutical compositions comprising these.

The invention relates to acid addition salts and/or solvates of [6-hydroxy-2-(4-hydroxyphenyl)benzol[b]thien-3-yl][4-[2-(1-piperidinyl)-ethoxy]phenyl-, raloxifene, having high availability from media comprising dilute hydrochloric acid, such as gastric juice. In addition useful crystal forms of the acid addition salts and/or solvates are disclosed.

In another aspect the invention relates to pharmaceutical composition for oral administration comprising said novel acid addition salts and/or solvates thereof, preferably in crystalline form. The pharmaceutical compositions according to the invention are useful because the high availability from dilute hydrochloric acid, such as gastric juice, secures a high and reliable release of the active ingredient, raloxifene, in the stomach of the patient to whom said pharmaceutical composition have been administered.

Further the invention provides an improved method for preparation and purification of said acid addition salts and/or solvates thereof, which method provides for a quick and highly efficient purification of the crude raloxifene product.

Background for the invention

Raloxifene, [6-hydroxy-2-(4-hydroxyphenyl)benzol[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, is a well known compound having antiestrogene and antiandrogene activity. Raloxifene or raloxifene hydrochloride has proved useful for the preparation of pharmaceutical compositions for the treatment of cancer, osteoporosis and cartilage degradation.

Raloxifene, [6-hydroxy-2-(4-hydroxyphenyl)benzol[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, is also known as 6-hydroxy-2-(4-hydrophenyl)-3-

[4-(2-piperidinoethoxy)-benzoyl]benzo-[b]-thiophene. Other names for raloxifene may also be found in the literature.

EP 62 503 A1 discloses benzothiophene compounds and process for preparing them. The disclosed compounds have antiestrogenic and antiandrogenic activity. Pharmaceutical preparation comprising said benzothiophene compounds are described, which preparations are useful for the treatment of cancers. A particular preferred compound is Raloxifene. Acid addition salts of the benzothiophene compounds with physiologically acceptable acids are also disclosed. As examples of physiologically acceptable acids are mentioned among others sulphuric acid, succinic acid and lactic acid.

In the manufacture of raloxifene the crude product in the reaction mixture was evaporated to dryness, redissolved and purified in several steps before the pure product was recovered as a crude product that was further purified to provide the desired compound.

The obtained free base was subsequent transformed into acid addition salts using usual techniques.

EP 584 952 discloses use of raloxifene or acid addition salts thereof for the treatment of osteoporosis. It is preferred to use an acid addition salt of raloxifene instead of raloxifene as a free base because the acid addition salts generally have improved dissolution properties compared to the free base. As examples of acids used for the acid addition salts are mentioned among others: hydrochloric acid, sulphuric acid, lactic acid, malonic acid and succinic acid. Raloxifene hydrochloride is the preferred acid addition salt.

EP 652 002 A1 discloses use or 2-phenyl-3-aroylbenzothiephenes or pharmaceutical acceptable acid addition salts thereof, such as raloxifene and raloxifene hydrochloride respectively, for the inhibition of cartilage degradation.

In WO 96/09045 raloxifene hydrochloride in crystalline form or as a solvate is described.

EP 910 369 discloses raloxifene hydrochloride in crystal form where the crystals are smaller than 50 microns, and EP 826 682 discloses raloxifene in

an amorphous form having enhanced solubility.

At present most commercial available pharmaceutical compositions comprising raloxifene as active ingredient comprises raloxifene hydrochloride, because raloxifene hydrochloride is fairly soluble in aqueous solvents whereas raloxifene as free base is only sparingly soluble in aqueous solvents.

Despite the extensive experimentation of increasing the bioavailability of raloxifene there is still a need for providing the active compound in a form having increased availability of the active compound in order to provide pharmaceutical preparations for oral administration, which composition have a high availability of the active compound raloxifene from the upper gastrointestinal tract.

Brief description of the invention

The present invention relates to raloxifene acid addition salts and/or solvates having a high availability in dilute hydrochloric acid or gastric juice.

The present inventors have surprisingly discovered that the raloxifene acid addition salts and solvates according to the invention have high bioavailability of the active compound soon after ingestion. In particular the raloxifene salts and/or solvates according to the invention have improved intrinsic dissolution properties in the presence of hydrochloric acid such as in gastric juice, compared with the commonly used raloxifene acid addition salt, raloxifene hydrochloride.

In a further aspect the invention relates to new and particular useful crystal forms of said novel raloxifene acid addition salts or solvates thereof.

In an even further aspect the invention relates to pharmaceutical compositions comprising said novel raloxifene acid addition salts and solvates thereof, which compositions after the ingestion thereof is capable of releasing the active compound raloxifene in higher amounts, compared with the frequently used compound raloxifene hydrochloride.

A further aspect of the invention relates to a new and improved method for preparation of raloxifene lactate.

Short description of the figures

Figure 1 shows a differential scanning calorimetric chart (DSC) for raloxifene DL-lactate ~~hemihydrate~~. The chart was recorded at a rate of 20°C/min.

Figure 2 shows the X-ray diffraction pattern for crystalline raloxifene DL-lactate ~~hemihydrate~~.

Figure 3 shows a DSC for raloxifene L-lactate hemihydrate. The chart was recorded at a rate of 20°C/min.

Figure 4 shows the X-ray diffraction pattern for crystalline raloxifene L-lactate hemihydrate.

Figure 5 shows a DSC for raloxifene L-lactate ~~¼ hydrate~~. The chart was recorded at a rate of 20°C/min.

Figure 6 shows the X-ray diffraction pattern for crystalline raloxifene L-lactate ~~¼ hydrate~~.

Figure 7 shows the Intrinsic Dissolution Rate for raloxifene succinate compared with raloxifene hydrochloride.

Figure 8 shows the Intrinsic Dissolution Rate for raloxifene DL-lactate ~~hemihydrate~~ compared with raloxifene hydrochloride.

Figure 9 shows the Intrinsic Dissolution Rate for raloxifene L-lactate ~~¼ hydrate~~ compared with raloxifene hydrochloride.

Figure 10 shows the Intrinsic Dissolution Rate for raloxifene L-lactate hemihydrate compared with raloxifene hydrochloride.

Figure 11 shows the Intrinsic Dissolution Rate for raloxifene malonate compared with raloxifene hydrochloride .

Figure 12 shows the Intrinsic Dissolution Rate for raloxifene sulphate compared with raloxifene hydrochloride.

Detailed description of the invention

The inventors have realized that even though raloxifene hydrochloride is fairly soluble in aqueous media the solubility appear to decreases significant in aqueous media comprising hydrochloric acid.

By the term "dilute hydrochloric acid" or "media comprising hydrochloric acid" as used herein is meant an acidic aqueous solution containing chloride ions. Gastric juice is a preferred example of dilute hydrochloric acid.

The skilled person will appreciate that gastric juice contains hydrochloric acid. Further the skilled person will appreciate that the composition of gastric juice apart from individual variations depends on various factors such as time of day, time since last meal and size and composition of said last meal. However for the purpose of the present description, the gastric juice can be regarded as a dilute solution of hydrochloric acid usually having a pH value in the range of approximately 1-3, possible also containing sodium chloride in an amount of 1-3 % w/w. In the duodenum and the upper part of the small intestines the pH raises up to approximately 4-6 or even higher.

The raloxifene acid addition salts and/or solvates thereof according to the invention have dissolution properties in dilute hydrochloric that secure a high bioavailability of these compounds. In particular the compounds according to the invention have higher intrinsic dissolution rates in dilute hydrochloric acid compared with free raloxifene or raloxifene hydrochloride.

The terms "high availability", "high bioavailability" or grammatical equivalent expressions are according to the invention intended to mean that the raloxifene salts and/or solvates thereof are available for assimilation from the gastro intestinal tract to the circulation of the body in high amount soon after ingestion. In particular the raloxifene salts and/or solvates thereof have higher

bioavailability compared with the presently frequently used raloxifene compounds, i.e. raloxifene as free base or raloxifene hydrochloride.

In accordance with the present invention the term "upper gastrointestinal tract" is intended to mean the oesophagus, the stomach, the duodenum and the upper part of the small intestines. It is believed that the assimilation of raloxifene mainly takes place in the upper gastrointestinal tract.

The inventors have surprisingly discovered that acid addition salts and/or solvates thereof according to the invention appear to have a higher bioavailability from acidic solutions comprising sodium chloride compared to raloxifene as free base or raloxifene hydrochloride in crystalline or amorphous form. Consequently, pharmaceutical preparations for oral administration comprising acid addition salts and /or solvates thereof according to the invention will provide the active compound raloxifene faster and/or in an higher amount compared with pharmaceutical preparations comprising raloxifene hydrochloride or raloxifene as free base.

Thus in one aspect the invention provides pharmaceutical preparations for oral administration comprising a raloxifene acid addition salt and/or solvate thereof according to the invention as the active ingredient. These preparations provide the active compound raloxifene in a form having high bioavailability when said preparations are ingested and dispersed in gastric juice.

The high availability of the active compound secures that a therapeutic regimen using the pharmaceutical preparations according to the invention may be performed with higher accuracy because the attending physician will know that the complete dose or at least a major part thereof will be available for assimilation from the gastro intestinal tract soon after the ingestion the pharmaceutical preparations according to the invention.

Therefore pharmaceutical compositions comprising such compounds may provide for a higher efficiency of the of said compounds by the individuals to whom said compositions are administered, compared with corresponding pharmaceutical compositions based on raloxifene or raloxifene hydrochloride.

Thus the pharmaceutical preparations according to the invention provide a fast and high availability of the active compound in the stomach soon after intake of the preparation.

Alternatively or additionally, the high availability of the active compounds according to the invention may render the need for micronization superfluous, which micronization in the prior art have been used to increase the bioavailability of raloxifene compounds, cf. EP 910 369.

Therefore in one aspect the present invention relates to pharmaceutical compositions for oral administration comprising raloxifene acid addition salts and/or solvates thereof, having fast and high bioavailability of the active compound raloxifene.

According to the invention the acid addition salts and/or solvates of raloxifene is selected among the succinate, lactate, malonate or the sulphate.

The lactate may be in the D or L form or a mixture thereof such as racemic mixtures. Further the lactate may be isolated as a solvate.

Because succinic acid, malonic acid and sulphuric acid have two acid groups per molecule, compounds of these acids and raloxifene may be isolated as either mono or di acid addition salts and/or solvates thereof having either one or two raloxifene molecules per acid molecule respectively.

In a preferred embodiment the acid addition salt and/or solvates thereof according to the invention is raloxifene DL-lactate, and in a particular preferred embodiment the acid addition salt is raloxifene L-lactate.

The skilled person will appreciate that the acid addition salts according to the invention may be isolated as solvates, which in the present description is to be understood as compounds where solvate molecules are included in the solid compounds, usually in defined stoichiometric amounts.

For some compounds more that one solvate may be isolated, which solvates differ only with respect of the solvent incorporated in the solid and the number of solvate molecules per molecule of the acid addition salt.

Preferred solvates according to the invention are solvates with pharma-

ceutically acceptable solvents such as water or alcohols having less than 5 carbon atoms, even more preferred selected among water, methanol, ethanol, propanol and 2-propanol.

Examples of solvates according to the invention include raloxifene L-lactate hemihydrate, raloxifene D-lactate hemihydrate, raloxifene DL-lactate hemihydrate, raloxifene L-lactate ¼-hydrate, raloxifene D-lactate ¼-hydrate, raloxifene DL-lactate ¼-hydrate and raloxifene sulphate (2-propanol solvate).

Preferred compounds according to the invention include raloxifene D-lactate hemihydrate, raloxifene DL-lactate hemihydrate, raloxifene L-lactate hemihydrate and raloxifene L-lactate ¼-hydrate, where raloxifene L-lactate hemihydrate and raloxifene L-lactate ¼-hydrate is particular preferred.

It is well known that organic compounds may be isolated in crystalline form or in amorphous form. Generally it is preferred to provide compounds in crystalline form because crystallisation usually is accompanied by a purification of the compound, and further, because crystals are more well defined solids than amorphous materials the properties of compounds in crystalline form varies less than materials in amorphous form.

Therefore the raloxifene acid addition salts and/or solvates according to the invention in crystalline form provides another aspect of the invention.

The raloxifene acid addition salts in crystalline form according to the invention are raloxifene lactate, raloxifene malonate and raloxifene succinate, which all exist as distinct crystalline compounds, and raloxifene sulphate, which may be isolated in crystalline form as a 2-propanol solvate having one molecule of 2-propanol incorporated per two raloxifene molecules.

For some of the raloxifene acid addition salts and/or solvates thereof according to the invention more that one crystal form may be possible, where the different crystal forms may be prepared dependent on the solvent, temperature etc, as it will be known within the area.

Pharmaceutical preparations for oral administration comprising raloxifene salts and /or solvates thereof according to the invention may be pre-

pared using pharmaceutical techniques well known within the area e.g. from text books such as Remington's manual.

For example may the raloxifene compounds according to the invention be formed for oral administration into tablets, capsules etc. In forming the pharmaceutical preparations the compounds according to the invention may be mixed with usual fillers and excipiens, such as disintegration agents, lubricants, swelling agents. The preparations may also be coated according to well-known techniques.

Raloxifene acid addition salts and/or solvates may be prepared using methods known for the skilled person.

For example may any acid addition salt be converted into the free base and subsequently the free base may be converted into another acid addition salt by known procedures.

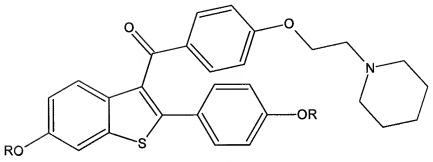
Usually raloxifene is prepared directly as raloxifene hydrochloride.

The present inventors have observed that in contrast to raloxifene and previously tested acid addition salts thereof e.g. raloxifene hydrochloride, raloxifene lactate can easily be crystallized in high yield and high purity from an alcoholic solution.

It has been realized that this property may be used for a quick and high efficient purification of raloxifene lactate from an intermediate in the synthesis of raloxifene.

Thus raloxifene lactate may be prepared directly without previous isolation of free raloxifene or raloxifene hydrochloride using the following procedure:

To a solution of the compound having the general formula I



Formula I

wherein R represents two independently selected hydroxyl protection groups,

in a solvent a suitable reagent is added in order to remove the protection groups. Next the pH of the mixture is adjusted to neutral reaction using lactic acid, and thereafter raloxifene lactate may be precipitated and isolated.

This procedure according to the invention is beneficial because raloxifene lactate is easily crystallized from such a mixture, particular if the solvent is an alcohol having 1-5 carbon atoms. The easy crystallisation of raloxifene lactate represents a high and easy purification of the raloxifene from the reaction mixture. The crystallized raloxifene lactate may be further purified by recrystallization from an alcohol.

The compound having the formula I is known within the art from e.g EP 875 511 A1, where it is called formula VII, and from EP 62 503, where it is prepared by the reaction scheme (B).

The group R may be any hydroxyl protection group known to the skilled person. For example, R may be selected from C_1–C_4 alkyl, C_5-C_7 cycloalkyl, benzyl $-COR^2$ or SO_2R^2, wherein R^2 is C_1–C_4 primary or secondary alkyl, C_1-C_3 fluoroalkyl, C_1-C_3 chloroalkyl, C_1-C_4 alkylphenyl, C_1-C_4 alkoxyphenyl, mono- or dinitrophenyl or mono- or di(chloro or fluoro)phenyl.

The two R groups may be the same or different. It is preferred that the two R groups are selected so that the similar conditions are needed to remove the two groups.

The term "neutral reaction" is intended to mean that the mixture has a pH value in the range of 6-8, preferably 7.0-7.5.

The chemical used to remove the protection groups may be any chemical known to be able to remove the particular used protection groups. It is within the skills of the practitioner to select a suitable chemical to remove the protection group for each selected protection group.

The solvent used for the reaction may in principle be any solvent that is capable of dissolving the reagents and does not participate in reactions with any of the ingredients of the reaction mixture under the conditions applied. Preferred solvents are alcohols having 1 to 5 carbon atoms. Particular preferred solvents are monovalent alcohols having 1 to 5 carbon atoms, where methanol, ethanol, propanol and 2- propanol are the most preferred solvents.

The obtained raloxifene lactate may be recrystallized in order to obtain the compound in even higher purity.

As solvent for the crystallization may in principle be used any alcohol having suitable melting and boiling temperatures. Alcohols having 1 to 5 carbon atoms and one hydroxyl group are preferred.

As examples of preferred alcohols can be mentioned methanol, ethanol, propanol, 2-propanol, butanol, 2-butanol, neobutyl alcohol, pentanol, 2-pentanol and 3-pentanol.

It is within the abilities of the skilled practitioner to select a suitable solvent for crystallization of particular selected compound of the invention.

Ethanol is a particular preferred alcohol.

The concentration of alcohol in the crystallization mixture should be higher that 90%, preferably higher that 95%. A particular preferred solvent for the crystallisation reaction is 96% ethanol.

The crystallisation may be performed using procedures known within the area. Further as it will be known for the skilled person it may be advantageous to add seeding crystals to the crystallization mixture to promote crystallisation.

Thus in another aspect the invention relates to a method for purification of raloxifene lactate from an alcoholic solution of raloxifene comprising addition of lactate, adjusting pH and temperature of the obtained mixture and isolation of the formed crystalline raloxifene lactate.

In a preferred embodiment the alcoholic solution of raloxifene is the reaction mixture of the synthesis of raloxifene if necessary after a change of solvent.

The invention is further illustrated by way of examples, which are solely provided for illustration and should not be considered at limiting in any way.

EXAMPLES

Example 1

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, succinate; Raloxifene succinate.

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

1 L of a solution of 70.85 g (0.6 mol) succinic acid in 2-propanol/water (80:20) is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white/yellowish crystals. The product is now washed 2 times with 40 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 178.5 g crude product.

The crude product is stirred with 890 ml of water for 3 hours and then filtered

off and washed 3 times with 100 ml of water. The product is dried in vacuo at 55-65 °C for 16 hours to give 89.7 g (77.3% yield) of product.

Mp: dec. > 195 °C, mp. ~ 225 °C

Elemental analysis $C_{33}H_{33}NO_8S$:

Calculated: C: 64.96% H: 5.62% N: 2.37% S: 5.42%

Found: C: 65.64% H: 5.49% N: 2.60% S: 5.99%

IR:

3406 cm $^{-1}$, 3145 cm $^{-1}$, 2945 cm^{-1}, 2691 cm $^{-1}$, 1642 cm $^{-1}$, 1597 cm $^{-1}$, 1541 cm $^{-1}$, 1501 cm $^{-1}$, 1457 cm $^{-1}$, 1430 cm $^{-1}$, 1421 cm $^{-1}$, 1356 cm $^{-1}$, 1259 cm $^{-1}$, 1234 cm $^{-1}$, 1171 cm $^{-1}$, 1125 cm $^{-1}$, 1108 cm $^{-1}$, 1079 cm $^{-1}$, 1047 cm $^{-1}$, 1038 cm $^{-1}$, 907 cm $^{-1}$, 839 cm $^{-1}$, 807 cm $^{-1}$, 623 cm $^{-1}$

XRD:

D	2Theta	I(rel)	I(abs))	FWHM
13.195230	**6.6933**	**20.78**	**8475**	**0.1400**
9.695642	**9.1137**	**13.43**	**5476**	**0.0300**
9.304945	**9.4972**	**18.19**	**7419**	**0.1300**
8.394523	**10.5300**	**13.26**	**5407**	**0.1000**
7.944460	**11.1283**	**14.15**	**5768**	**0.1000**
7.708667	**11.4699**	**17.61**	**7180**	**0.1200**
7.526675	**11.7482**	**12.32**	**5023**	**0.0898**
7.323294	**12.0756**	**15.22**	**6205**	**0.1000**
7.160495	**12.3512**	**13.04**	**5316**	**0.0800**

6.926815	12.7696	23.68	9655	0.1300
6.606409	13.3917	29.08	11856	0.1400
6.463392	13.3894	14.45	5891	0.0898
6.285432	14.0789	21.24	8662	0.1200
6.127742	14.4432	63.63	25947	0.1200
5.961999	14.8469	15.55	6342	0.0900
5.875574	15.0665	15.77	6430	0.0898
5.788967	15.2933	16.15	6585	0.1400
5.624221	15.7441	34.74	14167	0.1200
5.453763	16.2394	22.89	9334	0.1300
5.276560	16.7887	12.71	5182	0.1200
5.095057	17.3913	14.19	5786	0.1100
5.020392	17.6520	11.12	.4535	0.0898
4.835944	18.3309	18.30	7461	0.1200
4.765096	18.6059	18.62	7591	0.1100
4.630456	19.1519	65.88	26864	0.1600
4.525518	19.6003	15.16	6180	0.0800
4.484997	19.7792	24.48	9982	0.1000
4.376528	20.2745	18.78	7659	0.1000
4.352225	20.3889	19.11	7790	0.1000
4.227757	20.9959	29.39	11984	0.1000
4.191265	21.1808	56.82	23171	0.0800
4.158052	21.3520	40.16	16377	0.0898
4.101947	21.6475	17.14	6988	0.0800
4.062068	21.8626	19.79	8072	0.1000
4.010082	22.1496	11.70	4771	0.0600
3.921660	22.6556	100.00	40776	0.1300
3.860487	23.0194	29.04	11842	0.1100
3.813566	23.3066	19.25	7850	0.1100
3.732687	23.8189	19.33	7884	0.1300

3.694791	24.0669	22.47	9161	0.1100
3.644300	24.4054	18.84	7680	0.1400
3.544078	25.1067	13.63	5556	0.0700
3.496160	25.4565	16.28	6637	0.0898
3.446458	25.8299	20.36	8300	0.2100
3.398344	26.2021	12.35	5036	0.1200
3.373032	26.4022	8.82	3597	0.0898
3.305938	26.9481	14.08	5741	0.1100
3.281940	27.1489	10.08	4112	0.0898
3.260437	27.3314	9.66	3937	0.0898
3.227083	27.6194	19.22	7838	0.1200
3.179256	28.0434	16.28	6640	0.2600
3.146269	28.3435	8.89	3627	0.0898
3.121159	28.5764	9.58	3907	0.0900
3.097691	28.7975	10.64	4337	0.0400
3.074307	29.0213	19.64	8008	0.1200
3.032262	29.4328	10.17	4148	0.1300
3.010128	29.6541	9.43	3847	0.0898

Example 2

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, malonate; Raloxifene malonate.

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep

red solution appears. Reminiscence of insoluble product may be filtered off.

260 ml of a solution of 62.76 g (0.6 mol) malonic acid in 2-propanol/water is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white/yellowish crystals. The product is now washed 2 times with 40 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 182.4g crude product.

The crude product is stirred with 912 ml of water for 3 hours and then filtered off and dried in vacuo at 55-65 °C for 16 hours to give 98.7g (87.2% yield) of crude product. The crude product is boiled for 5 minutes in 500 ml 2-propanol and then cooled at 10 °C for 30 minutes. The product is filtered off and washed with 100 ml 2-propanol and then dried in vacuo to give 90.8g (97%) of the product.

Mp: . 226-227 °C

Elemental analysis $C_{32}H_{31}NO_8S$:

Calculated: C: 64.46% H: 5.41% N: 2.42% S: 5.55%

Found: C: 64.86% H: 5.55% N: 2.57% S: 5.87%

IR:

3388 cm $^{-1}$, 3199 cm $^{-1}$, 2950 cm $^{-1}$, 2683 cm $^{-1}$, 2543 cm $^{-1}$, 1643 cm $^{-1}$, 1597 cm $^{-1}$, 1539 cm $^{-1}$, 1502 cm $^{-1}$, 1467 cm $^{-1}$, 1421 cm $^{-1}$, 1355 cm $^{-1}$, 1306 cm $^{-1}$, 1255 cm $^{-1}$, 1169 cm $^{-1}$, 1038 cm $^{-1}$, 952 cm $^{-1}$, 907 cm $^{-1}$, 839 cm $^{-1}$, 808 cm $^{-1}$, 645 cm $^{-1}$, cm $^{-1}$, 623 cm $^{-1}$

XRD:

D	2Theta	I(rel)	I(abs)	FWHM
14.385166	6.1391	36.51	6471	0.0100
13.125024	6.7292	38.91	6896	0.1300
10.305386	8.5734	37.32	6614	0.1700
9.279238	9.5236	39.85	7062	0.1300
8.860721	9.9745	34.60	6133	0.0900
8.510328	10.3863	33.27	5895	0.0900
8.314361	10.6318	33.02	5852	0.0800
7.947949	11.1234	41.61	7375	0.1600
7.265135	12.1727	35.79	6343	0.1300
6.882996	12.8512	29.65	5254	0.0300
6.537915	13.5326	60.19	10667	0.1800
6.258251	14.1404	61.12	10833	0.2100
6.003203	14.7444	31.92	5657	0.1200
5.877911	15.0605	29.17	5170	0.0600
5.794580	15.2784	29.33	5198	0.0200
5.663226	15.6349	49.63	8796	0.1300
5.550457	15.9547	36.61	6487	0.0800
5.354103	16.5438	55.84	9897	0.2200
5.134028	17.2583	30.18	5349	0.1378
5.023848	17.6397	55.21	9784	0.2100
4.836637	18.3283	36.13	6404	0.1400
4.700761	18.8628	71.64	12696	0.1600
4.644808	19.0922	86.46	15323	0.1500
4.538522	19.5436	61.36	10874	0.1300
4.472256	19.8361	50.40	8931	0.1000
4.347111	20.4132	37.86	6709	0.1000

	4.247918	20.8951	88.12	15616	0.2300
	4.161428	21.3344	73.93	13101	0.1600
	4.085803	21.7341	37.19	6591	0.1100
	4.019584	22.0966	35.60	6309	0.1500
	3.921695	22.6554	100.00	17722	0.1700
	3.765729	23.6059	50.70	8986	0.2000
	3.703455	24.0097	34.79	6166	0.1200
	3.638542	24.4446	47.30	8382	0.1900
	3.499221	25.4339	44.29	7849	0.2000
	3.426872	25.9801	43.63	7732	0.2200
	3.292398	27.0610	23.39	4145	0.1000
	3.253755	27.3886	25.03	4435	0.1400
	3.192249	27.9269	22.18	3931	0.1400
	3.094846	28.8246	28.68	5083	0.3000
	3.034329	29.4123	27.30	4338	0.1900

Example 3

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, sulphate (2-propanol solvat); Raloxifene sulphate (2-propanol solvate).

3.79g (~0.06 mol) pulverized potassium hydroxide (>85%) is dissolved in 125 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 10g (0.0196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

A solution of 6.5g 96% (0.6 mol) sulphuric acid in 15 ml 2-propanol and 12 ml

of water is added with violent stirring during 1-1.5 hours (weakly exothermic). The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white crystals. The product is now washed 2 times with 4 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 15g crude product.

The crude product is stirred with 76 ml of water for 3 hours and then filtered off and washed 3 times with 100 ml of water. The product is dried in vacuo at 55-65 °C for 16 hours to give 8.6g (% yield) of product. The product is boiled with 38 ml of 2-propanol for 5 minutes and then cooled on to 0-5°C for 30 minutes and filtered. The product is washed with 2 times with 5 ml 2-propanol, and dried in vacuum at 70-75 °C.

Mp: . 262-263 °C

Elemental analysis $C_{59}H_{64}N_2O_{13}S_3$:

Calculated: C: 64.46% H: 5.41% N: 2.42% S: 5.55%

Found: C: 64.86% H: 5.55% N: 2.57% S: 5.87%

IR:

3199 cm $^{-1}$, 2963 cm $^{-1}$, 2723 cm $^{-1}$, 2693 cm $^{-1}$, 2659 cm $^{-1}$, 2559 cm $^{-1}$, 1653 cm $^{-1}$, 1597 cm $^{-1}$, 1547 cm $^{-1}$, 1501 cm $^{-1}$, 1467 cm $^{-1}$, 1437 cm $^{-1}$, 1419 cm $^{-1}$, 1344 cm $^{-1}$, 1308 cm $^{-1}$, 1268 cm $^{-1}$, 1251 cm $^{-1}$, 1233 cm $^{-1}$, 1167 cm $^{-1}$, 1037 cm $^{-1}$, 1020 cm $^{-1}$, 952 cm $^{-1}$, 907 cm $^{-1}$, 839 cm $^{-1}$, 823 cm $^{-1}$, 809 cm $^{-1}$, 627 cm $^{-1}$, 524 cm $^{-1}$.

XRD:

D	2Theta	I(rel)	I(abs)	FWHM
14.374007	6.1439	26.57	5009	0.0900
10.303750	8.5748	29.62	5583	0.1300
9.201529	9.6042	26.22	4942	0.1100
8.871726	9.9621	29.84	5624	0.1300
8.569965	10.3138	22.25	4195	0.0400
8.320378	10.6241	25.97	4896	0.1200
7.945119	11.1274	38.65	7286	0.1300
7.514174	11.7678	20.56	3876	0.1041
7.205108	12.2745	25.04	4721	0.1400
6.537437	13.5336	66.78	12590	0.1400
6.228787	14.2076	21.88	4126	0.1100
5.628329	15.7325	20.71	3904	0.0900
5.540447	15.9837	27.40	5166	0.1100
5.322476	16.5489	64.98	12249	0.1500
5.138694	17.2425	21.65	4082	0.1100
5.020317	17.6522	64.05	12074	0.1400
4.706881	18.8381	100.00	18851	0.1300
4.618097	19.2036	60.47	11400	0.0800
4.538129	19.5453	59.35	11189	0.1100
4.471816	19.8381	67.03	12636	0.1200
4.261964	20.8255	54.78	10327	0.1100
4.204757	21.1121	51.35	9680	0.1600
4.156029	21.3625	46.65	8794	0.1041
4.093305	21.6938	25.93	4888	0.0900
4.035960	22.0058	24.21	4563	0.1800
3.937182	22.5651	25.37	4784	0.1200

3.835400	23.1721	22.17	4179	0.0900
3.796528	23.4127	40.94	7718	0.0900
3.767170	23.5978	61.03	11505	0.1100
3.691303	24.0899	20.10	3790	0.1500
3.639317	24.4393	47.20	8897	0.1200
3.590489	24.7769	28.23	5321	0.1600
3.511060	25.3467	29.66	5592	0.1100
3.478586	25.5873	23.70	4468	0.1041
3.416539	26.0601	37.38	7047	0.1900
3.355389	26.5436	20.28	3823	0.1300
3.314637	26.8760	17.08	3220	0.1200
3.271015	27.2413	15.24	2874	0.0600
3.252583	27.3987	14.71	2773	0.1041
3.100446	28.7714	23.04	4344	0.1200
3.079703	28.9694	19.73	3720	0.1041
3.033828	29.4172	29.23	5511	0.1300
3.009744	29.6580	15.28	2880	0.1041
2.937725	30.4024	13.30	2507	0.1700

Example 4

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, DL-lactate ~~hemihydrate~~; Raloxifene DL-lactate ~~hemihydrate~~.

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene

hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

A solution of 67.6 g 85% DL-lactic acid (0.6 mol) in 200 ml of 2-propanol is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white/yellowish crystals. The product is now washed 2 times with 40 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 109 g crude product.

The crude product is stirred with 545 ml of water for 3 hours and then filtered off and washed 2 times with 75 ml of water. The product is dried in vacuo at 75-80 °C for 16 hours to give 92.7g (83.9% yield) of product.

Mp: . 196-198 °C

Elemental analysis $C_{34}H_{33}NO_7S.(\frac{1}{2}H_2O)$:
Calculated: C: 65.00 % H: 5.98 % N: 2.45 % S: 5.60 %
Found: C: 65.07% H: 5.93 % N: 2.37 % S: 5.34 %

IR:

3385 cm^{-1}, 3223 cm^{-1}, 2940 cm^{-1}, 2675 cm^{-1}, 1641 cm^{-1}, 1598 cm^{-1}, 1542 cm^{-1}, 1502 cm^{-1}, 1467 cm^{-1}, 1421 cm^{-1}, 1349 cm^{-1}, 1307 cm^{-1}, 1253 cm^{-1}, 1171 cm^{-1}, 1123 cm^{-1}, 1038 cm^{-1}, 953 cm^{-1}, 908 cm^{-1}, 837 cm^{-1}, 808 cm^{-1}, 649 cm^{-1}, 623 cm^{-1}, cm^{-1}, 532 cm^{-1}, 514 cm^{-1}.

The product was further analysed using differential scanning calorimetry using a METTLER TOLEDO STAR® system, according to the instructions of the manufacturer. The differential scanning calorimetric chart (DSC) is shown in figure 1.

Further the product was analysed by X-ray diffraction analysis using the STOE

Powder diffraction system. The result is shown in figure 2, and is also listed numerically below.

XRD:

D	2Theta	I(rel)	I(abs)	FWHM
13.595814	6.4959	28.40	12683	0.1400
10.855533	8.1382	16.15	7211	0.1200
9.849394	8.9711	32.17	14369	0.1000
9.534325	9.2682	66.95	29898	0.1300
8.150249	10.8465	45.20	20188	0.1300
7.240730	12.2138	63.53	28374	0.1400
6.769843	13.0670	18.42	8227	0.1500
6.272666	14.1077	75.67	33794	0.1900
5.818832	15.2143	13.28	5933	0.2000
5.657337	15.6513	18.07	8070	0.1300
5.505030	16.0872	10.51	4692	0.1000
5.261933	16.8357	17.48	7806	0.1400
5.089504	17.4104	16.14	7210	0.1000
5.001569	17.7189	41.94	18732	0.0900
4.958950	17.8725	29.16	13023	0.1148
4.797388	18.4795	19.39	8660	0.1100
4.669322	18.9910	49.20	21972	0.1400
4.574684	19.3876	63.21	28227	0.1000
4.533019	19.5676	44.94	20071	0.1148
4.440548	19.9792	32.70	14604	0.1200
4.301886	20.6301	100.00	44659	0.1500

4.155406	21.3657	78.00	34833	0.1600
4.059049	21.8797	27.53	12296	0.1800
3.960846	22.4285	25.59	11427	0.1000
3.907408	22.7393	83.48	37282	0.1200
3.865461	22.9894	16.46	7350	0.1148
3.828892	23.2120	17.46	7798	0.0900
3.773130	23.5599	50.71	22649	0.1200
3.716486	23.9243	23.06	10300	0.1300
3.652238	24.3515	15.79	7053	0.1800
3.584725	24.8174	12.91	5764	0.1500
3.486791	25.5261	30.45	13600	0.1200
3.439149	25.8858	22.21	9919	0.1300
3.396267	26.2184	17.86	7978	0.1100
3.370045	26.4261	12.48	5572	0.1148
3.329320	26.7553	9.21	4113	0.1100
3.292728	27.0582	11.81	5274	0.1000
3.278070	27.1815	11.25	5026	0.1148
3.218620	27.6935	21.24	9485	0.1900
3.167986	28.1452	13.80	6162	0.0900
3.143230	28.3715	30.33	13546	0.1000
3.095423	28.9191	14.02	6260	0.1200
3.024921	29.5058	11.56	5161	0.1400
3.007253	29.6831	13.40	5984	0.1300

Example 5

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, L-lactate hemihydrate; Raloxifene L-lactate hemihydrate.

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

A solution of 67.6 g 85% L-lactic acid (0.6 mol) is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours, and the precipitate is filtered off as white/yellowish crystals. The product is now washed 2 times with 40 ml 2-propanol and then dried in vacuo at 55-65 °C for 16 hours to give 109 g crude product.

The crude product is stirred with 545 ml of water for 3 hours and then filtered off and washed 2 times with 75 ml of water. The product is dried in vacuo at 75-80 °C for 16 hours to give 92.7g (83.9% yield) of product.

Mp: . 134-136°C

Elemental analysis $C_{31}H_{33}NO_7S$ (½H_2O):

Calculated: C: 65.00 % H: 5.98 % N: 2.45 % S: 5.60 %

Found: C: 65.08% H: 6.14 % N: 2.58 % S: 5.78 %

IR:

3167 cm^{-1}, 2934 cm^{-1}, 1641 cm^{-1}, 1627 cm^{-1}, 1593 cm^{-1}, 1543 cm^{-1}, 1500 cm^{-1}, 1469 cm^{-1}, 1433 cm^{-1}, 1350 cm^{-1}, 1314 cm^{-1}, 1259 cm^{-1}, 1170 cm^{-1}, 1128 cm^{-1}, 1103 cm^{-1}, 1033 cm^{-1}, 908 cm^{-1}, 836 cm^{-1}, 809 cm^{-1}.

The product was analysed using differential scanning calorimetry using a METTLER TOLEDO STAR® system, according to the instructions of the manufacturer. The differential scanning calorimetric chart (DSC) is shown in figure 3.

Further the product was analysed by X-ray diffraction analysis using the STOE Powder diffraction system. The result is shown in figure 4, and is also listed numerically below.

XRD:

D	2Theta	I(rel)	I(abs)	FWHM
14.639874	6.0322	17.56	6122	0.1200
13.207421	6.6871	15.07	5254	0.1200
10.875932	8.1229	80.41	28029	0.1200
9.268456	9.5347	22.67	7903	0.1200
8.140638	10.8593	17.92	6247	0.1200
7.488503	11.8083	15.59	5433	0.1000
7.310331	12.0971	12.47	4347	0.0800
7.089508	12.4754	25.79	8991	0.1000
6.931874	12.7603	12.78	4454	0.0900
6.723932	13.1566	27.83	9701	0.1300
6.551458	13.5045	14.20	4949	0.0900
6.359432	13.9143	30.57	10656	0.1100
6.130010	14.4378	21.33	7435	0.1300
5.853018	15.1249	36.40	12687	0.1100
5.626204	15.7385	15.49	5401	0.1300
5.507643	16.0795	23.25	8106	0.1000
5.447238	16.2590	13.21	4606	0.0870

5.224449	16.9573	19.21	6697	0.1100
5.160516	17.1690	17.10	5961	0.0870
5.083475	17.4312	14.74	5137	0.1100
4.954247	17.8896	19.64	6848	0.1000
4.863750	18.2252	28.34	9879	0.0800
4.805168	18.4494	46.26	16125	0.0700
4.756883	18.6383	49.99	17425	0.0800
4.656926	19.0420	19.10	6659	0.1900
4.630194	19.1530	17.96	6260	0.0870
4.566015	19.4248	21.34	7438	0.1000
4.487514	19.7680	12.76	4447	0.1000
4.347753	20.4101	11.69	4074	0.1100
4.301465	20.6322	19.17	6682	0.0900
4.224555	21.0120	14.55	5072	0.0870
4.186561	21.2049	23.33	8134	0.1700
4.065767	21.8425	26.06	9084	0.1000
4.015560	22.1190	17.10	5929	0.1000
3.976949	22.3365	14.98	5223	0.0500
3.935785	22.5732	34.50	12028	0.1100
3.867038	22.9799	100.00	34859	0.1000
3.779481	23.5198	40.14	13991	0.0800
3.742319	23.7567	59.68	20805	0.1000
3.710418	23.9640	13.17	4591	0.0870
3.645564	24.3968	11.19	3902	0.0800
3.621808	24.5593	18.71	6524	0.1000
3.552536	25.0459	16.01	5581	0.1000
3.516088	25.3098	13.46	4691	0.0600
3.498357	25.4402	12.66	4413	0.0700
3.467075	25.6737	10.74	3745	0.0500
3.418947	26.0414	21.49	7491	0.1000

3.395298	26.2260	12.12	4225	0.0870
3.369948	26.4268	15.48	5369	0.0700
3.358554	26.5181	14.33	4995	0.0600
3.244985	27.4641	11.90	4149	0.0700
3.229427	27.5990	9.63	3356	0.0870
3.177657	28.0578	15.07	5253	0.1200
3.144884	28.3562	32.65	11381	0.1000
3.106130	28.7176	9.83	3425	0.0800
3.082970	28.9380	9.00	3138	0.0870
3.056106	29.1980	8.56	2984	0.0870
3.032184	29.4335	8.74	3048	0.1100
2.994539	29.8121	8.27	2884	0.0700
2.979114	29.9700	9.26	3229	0.0800
2.924922	30.5387	9.19	3203	0.1800
2.870290	31.1346	16.32	5689	0.1400
2.828902	31.6019	13.59	4737	0.1100
2.762611	32.3808	10.83	3775	0.1000

Example 6

[6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-,; Raloxifene L-lactate ~~(1/4 H_2O)~~.

37.9g (~0.6 mol) pulverized potassium hydroxide (>85%) is dissolved in 1250 ml 2-propanol, with stirring and addition of nitrogen, over approximately 30 minutes. 100g (0.196 mol) raloxifene hydrochloride is added in small portions in such a way that temperature is kept below 30 °C. After addition of raloxifene hydrochloride, the deep red suspension is stirred for 30-45 minutes until a deep red solution appears. Reminiscence of insoluble product may be filtered off.

A solution of 67.6g 85% L-lactic acid (0.6 mol) is added with violent stirring during 1-1.5 hours. The mixture is now stirred further at room temperature for 18 hours. If no or very little precipitate appears in the solution the reaction mixture is filtered and 2-propanol is evaporated off. To the reminisce is now added 150 ml of water with stirring and the precipitated product is collected by filtration and dried in vacuo at 55-65°C. Next the crude product is recrystallized from 160 ml 96% ethanol (if necessary seeding crystals are added) to give 62.8g (56.4%) of the product.

Mp: 171-173 °C :

Elemental analysis $C_{31}H_{33}NO_7S$~~.(1/4H_2O)~~:
Calculated: C: 65.52 % H: 5.94 % N: 2.47 % S: 5.64 %
Found: C: 65.50% H: 5.85 % N: 2.50 % S: 5.74 %

IR:
3159 cm^{-1}, 2935 cm^{-1}, 2806 cm^{-1}, 2672 cm^{-1}, 1643 cm^{-1}, 1598 cm^{-1}, 1574 cm^{-1}, 1547 cm^{-1}, 1501 cm^{-1}, 1466 cm^{-1}, 1422 cm^{-1}, 1347 cm^{-1}, 1308 cm^{-1}, 1269 cm^{-1}, 1229 cm^{-1}, 1171 cm^{-1}, 1119 cm^{-1}, 1067 cm^{-1}, 1037 cm^{-1}, 1006 cm^{-1}, 908 cm^{-1}, 835 cm^{-1}, 807 cm^{-1}, 665 cm^{-1}, 649 cm^{-1}, 634 cm^{-1}, 623 cm^{-1}, 513 cm^{-1}.

The product was analysed using differential scanning calorimetry using a METTLER TOLEDO STAR® system, according to the instructions of the manufacturer. The differential scanning calorimetric chart (DSC) is shown in figure 5.

Further the product was analysed by X-ray diffraction analysis using the STOE Powder diffraction system. The result is shown in figure 6, and is also listed numerically below.

XRD:

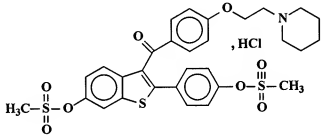
D	2Theta	I(rel)	I(abs)	FWHM
14.079244	**6.2726**	**45.93**	**16568**	**0.1300**
9.974912	**8.8580**	**32.43**	**11699**	**0.1100**
9.526523	**9.2758**	**71.31**	**25721**	**0.1200**
8.215598	**10.7600**	**47.82**	**17248**	**0.1100**
7.246270	**12.2045**	**80.04**	**28871**	**0.1100**
7.065557	**12.5178**	**16.17**	**5832**	**0.0700**
6.878001	**12.8606**	**22.74**	**8201**	**0.1200**
6.283709	**14.0828**	**66.27**	**23901**	**0.0800**
6.194698	**14.2862**	**53.98**	**19470**	**0.0984**
5.859529	**15.1080**	**11.17**	**4028**	**0.0984**
5.744935	**15.4112**	**16.16**	**5828**	**0.1200**
5.312222	**16.6751**	**18.02**	**6499**	**0.1200**
5.046910	**17.5585**	**34.26**	**12356**	**0.0900**
4.978933	**17.8001**	**54.66**	**19715**	**0.1000**
4.918535	**18.0205**	**17.40**	**6277**	**0.0984**
4.746264	**18.6804**	**26.77**	**9655**	**0.1000**
4.712771	**18.8143**	**46.35**	**16716**	**0.0900**
4.569429	**19.4101**	**57.60**	**20777**	**0.1000**
4.455985	**19.9093**	**53.60**	**19332**	**0.1200**
4.345589	**20.4204**	**12.70**	**4579**	**0.0900**
4.268096	**20.7952**	**86.33**	**31139**	**0.0900**
4.106332	**21.6241**	**20.17**	**7274**	**0.1100**
4.042283	**21.9710**	**22.73**	**8197**	**0.1200**
3.944656	**22.5218**	**23.46**	**8462**	**0.1000**
3.913129	**22.7056**	**100.00**	**36069**	**0.1100**

3.831706	23.1947	15.49	5586	0.0900
3.777075	23.5350	69.72	25148	0.1400
3.735872	23.7983	14.85	5358	0.0984
3.667856	24.2463	11.94	4305	0.0900
3.639035	24.4413	13.87	5001	0.0800
3.589918	24.7809	9.38	3383	0.0984
3.545715	25.0949	23.58	8505	0.0800
3.505655	25.3864	33.63	12131	0.1100
3.442223	25.8622	22.60	8152	0.1100
3.411017	26.1030	10.82	3901	0.0984
3.371851	26.4117	44.16	5108	0.1000
3.280618	27.1600	15.23	5494	0.1100
3.251104	27.4114	14.23	5134	0.0800
3.232072	27.5760	19.25	6943	0.1100
3.153056	28.2812	12.42	4479	0.1900
3.143130	28.3724	12.29	4432	0.0984
3.081939	28.9479	17.16	6189	0.2200
3.040378	29.3524	9.73	3510	0.1300
2.990508	29.8532	15.29	5514	0.1400
2.929711	30.4876	11.37	4102	0.1200
2.892397	30.8906	18.91	6822	0.1200
2.856192	31.2922	8.91	3214	0.1100
2.818108	31.7261	14.79	5336	0.2500
2.765584	32.3450	15.86	5720	0.1300

Example 7

Preparation of [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, L-lactate; Raloxifene L-lactate.

40g (0.06 mol) 6-methylsulphonyloxy-2-(4-methylsulphonyl-oxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl-, hydrochlo-rid, having the structural formula below



is suspended in 385 ml 2-propanol. 21.75g (0.33 mol) powdered 85% potassium hydroxide is added with stirring, and the mixture is heated to reflux for 2 hour. The deep red solution is cooled to room temperature, and a solution of 20.3 g 85% L-lactic acid (0.18 mol) is added with violent stirring during 1-1.5 hours, and thereafter the 2-propanol is evaporated off to give the crude product. The product is recrystallized from approximately 50 ml 96% ethanol to give the title compound.

Example 8 (Comparative example)

Dissolution of raloxifene hydrochloride in dilute hydrochloric acid or phosphoric acid

60 mg raloxifene HCl was transferred to a dissolution vessel containing one litre 0.1 M HCl. The mixture was vigorously mixed and left at room temperature over night. Subsequently the dissolution was evaluated visually. Very little of the initial added amount of raloxifene hydrochloride was dissolved shown by the presence of solid material at the bottom of the vessel and essentially no colouring of the fluid.

A similar dissolution test was performed using 60 mg raloxifene hydrochloride in 0.1 M phosphoric acid. In this case all raloxifene hydrochloride seemed to be dissolved indicated by the absence of solids on the bottom of the vessel and a strong yellow colouring of the fluid in the vessel.

Example 9

Dissolution of raloxifene acid addition salts or solvates in dilute hydrochloric acid or phosphoric acid

Using same procedures as in example 8, raloxifene succinate, raloxifene DL-lactate ~~hemihydrate~~, raloxifene L-lactate hemihydrate, raloxifene malonate and raloxifene sulphate (2-propanol solvate) were tested for dissolution in dilute hydrochloric acid or phosphorous acid.

All these tests showed complete dissolution shown be absence of solids in the vessel and strong colouring of the liquid.

Example 10

Intrinsic dissolution rate of raloxifene acid addition salts in dilute phosphoric acid compared with dilute hydrochloric acid.

Experimental set-up:

The intrinsic dissolution rate of raloxifene succinate, raloxifene DL-lactate ~~hemihydrate~~, raloxifene L-lactate ~~¼ hydrate~~, raloxifene L-lactate hemihydrate, raloxifene malonate, raloxifene sulphate (2-propanol solvate) and raloxifene hydrochloride were tested in dilute solutions of hydrochloric acid and in dilute solutions of phosphorous acid containing NaCl in amounts so the chloride ion concentration in each solution was 0.1 M. The tests were performed at 37 °C and at pH of 1, 2, 3, 4, and 5, respectively. The raloxifene hydrochloride salt used in these experiments was purchased from Otto Bradt GmbH (batch MA/RF/12003) while the rest of the raloxifene acid additions salts were prepared according to Example 1-6.

The experiments were carried out following the procedure of Rotation Disc Method (USP 1087) using Vankel VK 7000 Intrinsic dissolution apparatus (Vankel Technology group, W. Vankelion) equipped with Vankel 12-4120 intrinsic disc having a surface area of 0.5 cm^2, Vankel 12-4130 surface plate, Vankel 12-4140 punch, and Vankel shaft and holder (surface area: 0.5 cm^2) and operating at a rotation rate of 100 rpm.

The buffer solution is handled in a 750 ml measuring bottle, degassed and transferred into a dissolution vessel. Approximately 100 mg compound is weighed out and transferred into an intrinsic disc. Said disc is then assembled, and to said disc a disc is applied in the IR-press at a pressure of 5 kN for 1 minute. The disc is started and samples of 10 ml are collected by use of "pressure vials" after 1, 10, 20, 30, 45, and 60 minutes. The change of volume is corrected using the equation:

$$Q = Vs \times (sumCn - 1) + Cn \times Vt$$

wherein Q designates the volume at the time t, C designates the concentration of the sample n, Vt designates the volume of the liquid collected at the time t, and Vs designates the volume of the sample collected. The sample is measured

against a standard using HPLC. In these measurements a 5 microns 3.9 x 150 mm column filled with symmetrical material is employed and as eluant a 20 mM phosphate buffer KH_2PO_4, pH 6.8 mixed with acetonitrile and tetrahydrofuran in the ratio 55:35:10 is used.

Preparation of standard solution:

The standard is prepared by use of following procedure: 20 mg of salt is dissolved initially in 100 ml of MeOH and then 1 ml of this solution is transferred to a 50 ml flask with water and then 2 ml to a 20 ml flask of buffer in question.

Preparation of buffer solutions:

pH 1: a 0.1 M HCl is used.

0.025 M Phosphate buffer solution **pH 2.0:** 3.40 g of potassium dihydrogen phosphate is dissolved in 900 ml of water. Then pH is adjusted to 2.0 with phosphoric acid and diluted to 1000.0 ml with water. Exactly 5.85 g of NaCl is added to 1 L of buffer.

0.025 M Phosphate buffer solution **pH 3.0:** 3.40 g of potassium dihydrogen phosphate is dissolved in 900 ml of water. Then pH is adjusted to 3.0 with phosphoric acid and diluted to 1000.0 ml with water. Exactly 5.85 g of NaCl is added to 1 L of buffer.

0.022 M Phosphate buffer solution **pH 4.0:** 3.0 g of potassium dihydrogen phosphate is dissolved in 800 ml of water. Then pH is adjusted with 1 M potassium hydroxide and phosphoric acid and diluted to 1000.0 ml with water. Exactly 5.85 g of NaCl is added to 1 L of buffer.

0.02 M Phosphate buffer solution **pH 5.0:** 2.72 g of potassium dihydrogen phosphate is dissolved in 800 ml of water. Then pH is adjusted with 1 M potassium hydroxide and diluted to 1000.0 ml with water. Exactly 5.85 g of NaCl is added to 1 L of buffer.

Results

The results from above described experiment comparing the ID of the various raloxifene acid addition salts in dilute solutions of phosphorous acid and hydrochloric acid, respectively, is given in the table below. The numbers in the table represent the average of two measurements.

Buffer solution	Succi-nate	DL-lactate ~~hemi-hydrate~~	L-Lactate ~~¼-hydrate~~	L-lactate hemi-hydrate	Malo-nate	Sulphate	Hydro-chloride
Hydrochloride, pH 1	0.0550	0.0056	0.0035	0.0475	0.0229	0.0036	0.0022
Phosphate, pH 2	0.0228	0.0119	0.0028	0.0453	0.0173	0.0137	0.0026
Phosphate, pH 3	0.0271	0.0062	0.0067	0.0403	0.0148	0.0052	0.0022
Phosphate, pH 4	0.0127	0.0212	0.0324	0.0190	0.0136	0.0109	0.0022
Phosphate, pH 5	0.0119	0.0215	0.0247	0.0091	0.0112	0.0081	0.0044

The intrinsic dissolution rate (IDR) in (μmol/min*cm^2) of various acid addition salts of raloxifene determined by the method described above. The numbers represent the average of two measurements.

Graphic displays of the results are shown in the figures 7-12. The results show very clearly that the intrinsic dissolution rate is markedly higher for the raloxifene acid addition salts and/or solvates thereof according to the invention compared with raloxifene hydrochloride.